Cardiovascular determinants of life span

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Cardiovascular determinants of life span

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Abstract The prevalence of cardiovascular diseases rises with aging and is one of the main causes of mortality in western countries. In view of the progressively aging population, there is an urge for a better understanding of age-associated cardiovascular diseases and its underlying molecular mechanisms. The risk factors for cardiovascular diseases include unhealthy diet, diabetes, obesity, smoking, alcohol consumption, physical inactivity, and aging. Increased production of oxygen-derived free radicals plays an important role in mediating cardiovascular diseases. Oxidative stress affects the availability and/or balance of key-regulators of vascular homeostasis and favors the development of cardiovascular diseases. Reactive oxygen species are generated by different intracellular molecular pathways principally located in the cytoplasm and in the mitochondria. The mitochondrial protein p66Shc and the deacetylase enzyme SIRT1 were shown to be involved in different aspects of cardiovascular diseases. This review focuses on the latest scientific advances in understanding cardiovascular diseases associated to aging, as well as delineating the possible therapeutic implications of p66Shc and SIRT 1 in this process.

Keywords Oxidative stress · Blood pressure · Obesity · Diabetes mellitus · Mitochondria

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Introduction

To date, cardiovascular disease is the leading cause of death in western countries. Although the absolute incidence and mortality of cardiovascular disease are falling, figures are still very high. Thus, there is an urge for more efforts by the scientific community to identify new mediators and/or novel therapeutic targets for cardiovascular disease.

Cardiovascular disorders are a heterogeneous entity encompassing risk factors such as hypertension, diabetes, smoking, obesity, and aging, as well as true cardiac conditions such as coronary artery disease, infarction, and heart failure. However, certain traits seem to be a common denominator to different cardiovascular conditions. Usually, endothelial dysfunction is the earliest disturbance. However, it is rather difficult to be diagnosed before symptoms develop. The present nonexhaustive review discusses some of the latest scientific advances at the molecular level.

Elevated oxidative stress and vascular dysfunction

The endothelium, the innermost layer of the vascular wall, offers a primary protection against vascular dysfunction, occurrence of atherosclerosis, and thrombogenesis. Under physiological conditions, a balance between reactive oxygen species (ROS) damage and endothelial progenitor cell-mediated repair keeps the integrity of endothelium and maintains endothelial functions [20]. However, under pathophysiological conditions, this balance shifts towards ROS-induced damage, which is due to additional cellular damage by protein oxidation and/or decreased endothelial progenitor cells' function [6, 32] (Fig. 1).

Nitric oxide (NO), the principle endothelial-derived relaxing factor [38, 107], possesses inhibitory effects on

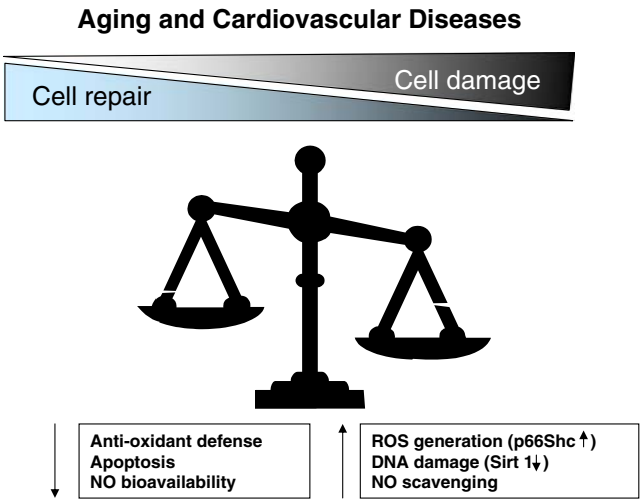

Fig. 1 With aging and cardiovascular diseases, the balance between noxious insults and protective systems is progressively lost favoring the development of endothelial dysfunction and vascular disease. *ROS* reactive oxygen species, *NO* nitric oxide

endothelium-derived contracting factors [38, 107]. When the release of NO is reduced and the production of endothelium-derived contracting factors is enhanced, endothelial dysfunction ensues [107]. In addition, NO plays a key role in preventing atherosclerosis by reducing the adhesion of platelets and leukocytes [8, 33] and by inhibiting the migration and proliferation of smooth muscle cells [69].

A large body of evidences reports a reduced blood flow in aged people or patients with hypertension, hypercholesterolemia, atherosclerosis, heart failure, or diabetes [56, 59, 83]. This phenomenon is also observed in pertinent animal models and is associated with a reduced NO bioavailability and/or an enhanced endothelium-dependent vasoconstriction [7, 43, 91, 108]. These studies confirm endothelial dysfunction observed in cardiovascular disorders in human.

The elevated levels of superoxide anion (O_2^-) observed under disease conditions are a crucial factor for the loss of NO availability in endothelial cells since the expression of endothelial nitric oxide synthase (eNOS) in diseases is either declined [26] or preserved [92]. Superoxide anion inactivates NO in a few seconds resulting in the generation of another highly reactive species, peroxynitrite ($ONOO^-$). Peroxynitrite penetrates across the phospholipid membrane and produces substrate nitration, thereby, damaging DNA [98], modifying lipoproteins by oxidation [82], disrupting mitochondrial function [57, 58, 97], and depleting plasma antioxidants [106].

The increased production of ROS under disease conditions is also implicated in proinflammatory processes by directly acting as second messengers. For instance, ROS activate NF-κB, a key transcription factor [27]. Activation of NF-κB, in turn, promotes the transcription of several critical genes for atherogenesis including cytokines such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and adhesion molecules (VCAM-1) [14, 28, 29, 39, 47, 50, 52]. Thus, oxidative stress is regarded as a key factor contributing to chronic inflammation [27].

Oxidative stress in cardiovascular disease

A large body of evidences underscores a critical role for oxygen free radicals in endothelial injury, aging, and cardiovascular diseases [17, 24, 31, 55, 107]. Aging shares several molecular features with cardiovascular diseases [16, 94]. The free radical theory of aging is widely accepted as the reference concept describing the mechanism underlying aging and aging-related diseases [26, 35, 41, 42, 75, 84, 105]. Increased production of ROS in aging is associated with enhanced $ONOO^-$ formation [105], up-regulated expression of inducible nitric oxide synthase (iNOS) [26], NAD(P)H oxidase [2], and/or a parallel down-regulation of antioxidants such as extracellular SOD [48] and decreased catalase activity [92].

The development of atherosclerosis is considered to be the result of chronic inflammation mostly induced by the increased production of ROS. The principal sources of free radical species in atherosclerosis are iNOS [30, 113], NAD(P)H oxidase [111], and/or cyclooxygenase-2 [5], since these proteins are expressed in atheromatous plaques. Importantly, ROS modify lipoproteins to the oxidized form, e.g., oxidized low-density lipoprotein (oxLDL), which has profound biological effects via the LOX-1 receptor in endothelial cells and the scavenger receptor-A in macrophages [3, 40, 100, 118]. In addition to the decrease in eNOS activity [36, 89, 101], oxLDL increases the expression of VCAM-1 and MCP-1 protein through NF-κB-mediated gene transcription [3, 22]. This implies an intricate ROS-mediated inflammation in the occurrence of atherosclerosis.

Diabetes is a major risk factor for cardiovascular diseases [31]. The increased production of free radicals observed in diabetes results from reduced activity of superoxide dismutase [19, 22, 89, 96, 101], reduced expression of heme oxygenase [19], as well as from enhanced expression of NAD(P)H oxidase [62, 69, 112] and cyclooxygenase [60, 61, 91]. In addition, the unique glycation reaction in diabetes generates, yet, more oxidative free radicals through intermediate compounds that in turn increase the levels of reactive oxygen species [31, 45, 46, 87, 88, 95, 103, 119, 121]. Dicarbonyl compounds such as methyglyoxal and 3-deoxyglucosone and intermediate products of glycation are typical examples. The serum

concentrations of both methyglyoxal and 3-deoxyglucosone are increased in patients with diabetes mellitus [99] indicating that free radicals play a crucial role in the pathogenesis of diabetes-associated complications [103, 114].

The ROS sensitive protein p66Shc

The mitochondrial adaptor protein p66Shc is regarded as an important mediator of aging since genetic deletion of p66Shc protein in the mouse causes lower levels of ROS and prolongs lifespan by 30% [66]. The mammalian Shc locus encodes for three different ShcA adaptor proteins with respective molecular masses of 46, 52, and 66 kDa. The splice variant p66Shc is the only isoform to participate in mitochondrial ROS generation and thus, to translate oxidative signals into apoptosis [12, 51, 66, 72]. In fact, in the absence of p66Shc, mitochondrial oxidative phosphorylation is reduced in favor of glycolysis. In light of its pivotal role in ROS generation, many efforts have been made to investigate the pathophysiological relevance of p66Shc in ROS-mediated diseases [18, 23].

The expression pattern of p66Shc protein in humans was studied in young people, elderly, and centenarians. The expression of p66Shc in fibroblasts was shown to increase with age [79] suggesting that the expression of p66Shc protein concurs with the process of aging. In human peripheral blood monocytes, p66Shc messenger RNA expression is enhanced in diabetic patients compared to healthy subjects [78]. Given the up-regulated expression of p66Shc in aged people and in diabetic patients, the hypothesis that this mitochondrial adaptor protein p66Shc is linked to aging and/or ROS-related diseases is widely accepted. Genetically modified mice are a useful tool to study the role of p66Shc protein under pathophysiological conditions since identical Shc genomic organization, transcript assembly, as well as, a high degree of amino acid identity have been reported in mice and in humans [67].

In adipose cell culture experiments, insulin treatment increased the production of ROS in brown preadipocytes from wild type mice, but not in those from p66Shc knockout mice. Reintroduction of p66Shc expression ex vivo restored the insulin-stimulated ROS production in preadipocytes of p66Shc knockout mice, confirming that p66Shc plays a crucial role in ROS production [9]. Further, p66Shc knockout mice are resistant to high fat diet-induced obesity, which is shown as increased basal metabolism, reduced fat development, and increased insulin sensitivity of peripheral tissues [9]. These results imply that p66Shc is an important mediator of insulin-signaling pathway, as well as energetic metabolism.

In line with the above, a blunted age-dependent and NO-mediated vasodilatation was maintained in the aorta of age-matched p66Shc knockout mice (Fig. 2) demonstrating that a preserved NO bioavailability in aged p66Shc knockout mice is due to lower aortic O_2^- levels and reduced aortic 3-nitrotyrosine content [37]. Preserved NO availability in aged p66Shc knockout mice was shown to be dependent on a reduced ROS production and a consequently reduced scavenging [37].

The beneficial effects of p66Shc protein deletions are also observed in apoE knockout mice [18, 71]. High fat diet induces comparably high levels of serum lipid in both control and p66Shc knockout mice. However, the level of lipid peroxidation is lower in p66Shc knockout mice compared to control mice. This suggests a putative role of p66Shc in the oxidation modification of lipoprotein. Seemingly, p66Shc knockout mice are protected from high fat diet-induced aortic lesion due to a decreased oxidative stress and a decreased formation of foam cells [71]. These data indicate that p66Shc takes part in the development of ROS-mediated atherosclerotic lesion.

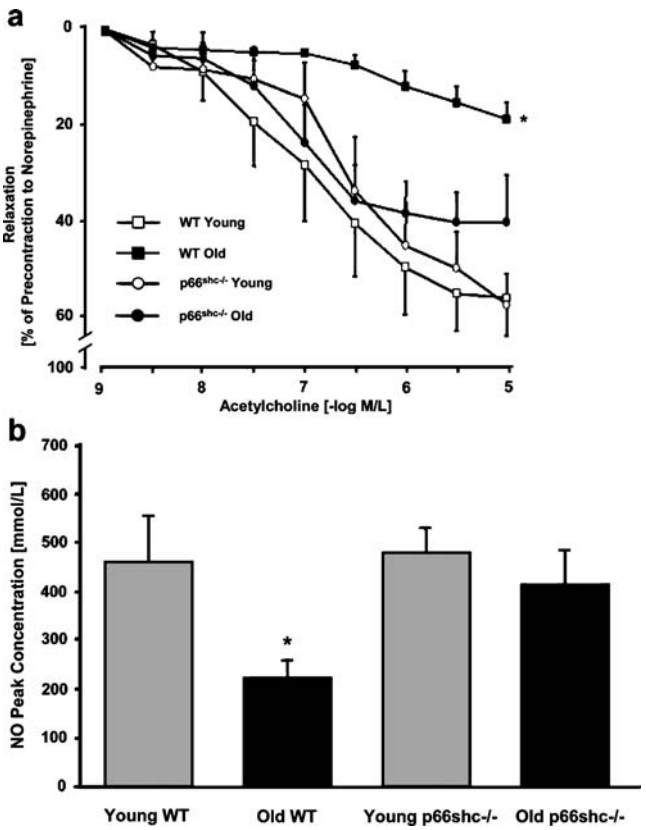

Fig. 2 **a** Age-induced changes in endothelium-dependent relaxation of WT and p66shc-/- aortas. Lines graph showing concentration–response curves to acetylcholine. Results are presented as mean± SEM; $n=7$ in each group. *M/L* indicates mol/L. The symbol (*) indicates $p<0.05$ versus young WT. **b** Bar graph showing *peak* concentrations of NO in young (*gray bars*) and old (*black bars*) WT and p66shc-/- mice, respectively. Results are presented as mean± SEM; $n=4$ to 6 in each group. The symbol (*) indicates $p<0.05$ versus young WT [84]

In line with the observation that p66Shc expression is increased in diabetic patients [78], the expressions of p66Shc protein is enhanced in the aorta and the renal cortex of streptozotocin-induced type I diabetic mice [19, 64]. Glucose levels in serum were comparable in diabetic p66Shc knockout and wild type mice [19, 64, 65], indicating that the deletion of p66Shc protein does not affect the diabetic condition and the hyperglycemia. Nevertheless, p66Shc knockout mice are protected from diabetes-induced endothelial dysfunction [19] and diabetic glomerulopathy [65], which is due to reduced production of ROS and a decreased cellular apoptosis (Fig. 3). The above-described data underscore the pivotal role of p66Shc in diabetes-induced ROS production [19].

The energy sensor—SIRT1

SIRT1 belongs to histone deacetylase class III, which reverses protein acetylation and promotes DNA stability. SIRT1 also deacetylates a number of nonhistone target protein, including tumor suppressor p53 protein [54, 109], members of the Forkhead transcription factor family (FoxO) [15, 73, 104, 116], stress response protein ku70 and NF-κB [21, 117], and metabolic regulator PCG-1α [86]. Owing to a unique nicotinamide adenine dinucleotide (NAD+)-dependent enzymatic activity, SIRT1 was recently considered as a promising therapeutic approach for aging and aging-associated cardiovascular diseases [93].

Starvation enhances the expression of SIRT1 protein in mouse liver and in human peripheral blood mononuclear cell, which returns to normal level upon feeding [73, 86]. The up-regulated SIRT1 protein deacetylates PGC-1 α in a NAD^+-dependent manner in both hepatic cells and mice livers, indicating a regulatory role of Sirt1 in the gluconeogenic/glycolytic pathway [86]. In a mouse model of chronic calorie restriction, which extends lifespan, the expression of SIRT1 protein is elevated in the calorie-restricted group [74]. Likewise, mice overexpressing SIRT1 share a similar phenotype to calorie-restricted mice, including lower body weight, lower cholesterol level, improved glucose homeostasis, and increased metabolic rate [13]. Thus, SIRT1 is an important mediator of the beneficial effects observed with calorie restriction and is probably involved in lifespan control.

The presence of SIRT1 protein was also observed in pancreatic β cell [70]. In cell culture experiments, inhibition of SIRT1 reduced the secretion of insulin suggesting that SIRT1is a possible target to insulin secretion [70]. In SIRT1 knockout mice, insulin levels are reduced in both normoglycemic and glucose tolerance experiments. Consistently, in a type II diabetic mouse, genetic up-regulation of SIRT1 [13, 76] or treated with resveratrol [68], a small molecule activator of SIRT1, enhances insulin secretion, and thus, improves glucose tolerance. These data underscore that the activator of SIRT1 is a potentially therapeutic principle for diabetes, especially for insulin-resistant type II diabetes.

SIRT1 also has beneficial effects on endothelial cells. In rat aorta, inhibition of SIRT1 ex vivo causes a blunted endothelium-dependent relaxation. Restoration of SIRT1 increases eNOS expression by deacetylation on both lysine 496 and 506 indicating that SIRT1 directly regulates eNOS [63]. In apoE knockout mice fed with high fat diet, the mouse overexpressing endothelial cell-specific SIRT1 maintains relaxation in the aorta accompanied by up-regulated eNOS and a retarded atherogensis [122]. This result confirms a protective role of SIRT1 and eNOS for the

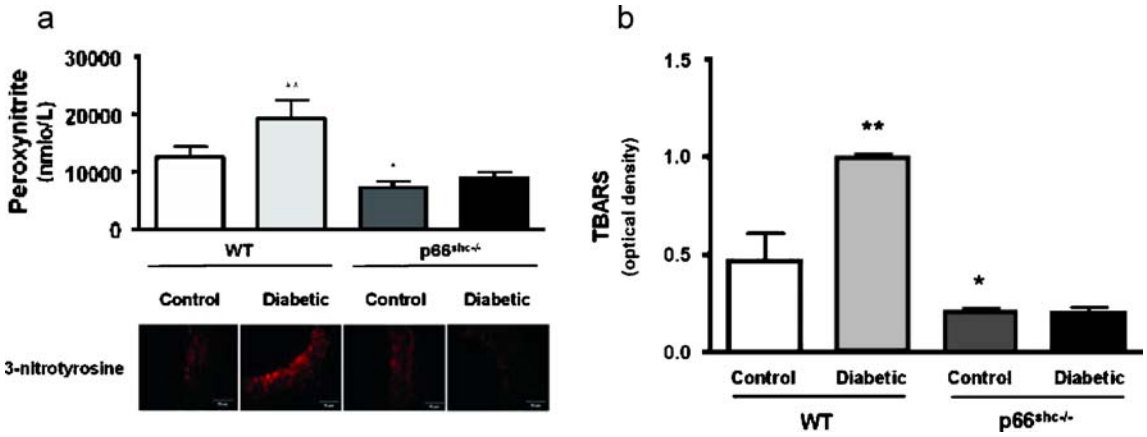

Fig. 3 **a** Bar graphs showing $ONOO^-$ levels determined by chemiluminescence. Results are presented as mean±SEM; $n=6$ in each group. $p<0.05$ versus control WT mice; $p<0.05$ versus control WT mice. Immunostaining of nitrotyrosine residues in aortas from control and diabetic WT and p66Shc-/- mice is shown. **b** Bar graphs showing thiobarbituric acid-reactive substances levels in aortas from control and diabetic WT and p66Shc-/- mice. Results are presented as mean±SEM; $n=4$ in each group. The symbol (*) indicates $p<0.05$ versus control WT mice; $p<0.05$ versus control WT [58]

development of atherosclerosis. Nevertheless, NO donor increases SIRT1 expression and delays cell senescence in human endothelial cells [77]. Calorie restriction fails to enhance SIRT1 expression in eNOS knockout mice [74], suggesting that NO may also directly modulate SIRT1 expression.

In the aorta of streptozotocin-induced diabetic mouse, the expression of SIRT1 protein is reduced accompanied by higher levels of acetylated p53 and p21 expression [76]. Resveratrol restores acetylated p53 and p21 in the aorta and thus, improves endothelial dysfunction by down-regulating ICAM-1 expression and inhibiting leukocyte rolling [76], These data suggest a protective role for SIRT1 in the pathogenesis of diabetic vascular dysfunction.

In transgenic mice with heart-specific overexpression of SIRT1, beneficial effects are observed only in animals with a slight or moderate up-regulation of SIRT1, which is due to an increased catalase expression through FoxO-dependent signaling. Furthermore, the heart-specific over-expression of SIRT1 retards aging of the heart and further protects the heart from paraquat-induced oxidative stress [4].

Clinical perspective

The proteins discussed in the present review represent different therapeutic targets for treatments of cardiovascular diseases, reducing cell damage or enhancing cell defenses.

The p66Shc protein is strongly linked to the generation of ROS. Genetic deletion of p66Shc prevents ROS-mediated cell damage and by doing so reduces cellular apoptosis. Since the antioxidant treatments proposed to decreases cardiovascular events failed to reduce the risk of cardiovascular events in large long-term clinical trials [53, 90, 110], the inhibition of p66Shc seems to be a more attractive therapeutic option to reduce oxidative stress in humans.

SIRT1 exerts multiple protective effects. Physical training is reported to restore SIRT1 protein in both heart and adipose tissue of aged mice [34] supporting the beneficial effect of exercise training [1, 10, 11, 34, 81, 85, 102]. Resveratrol, one of the polyphenolic compounds in grapes and wine, is reported as a small molecule activator of SIRT1 [44, 49]. Resveratrol increases insulin secretion in pancreatic β cells [68] and improves endothelial function in the aorta of diabetic mouse [76]. Besides, resveratrol reduces TNF-α-induced tissue factor expression through inactivation of NF-κB-mediated transcription [80] and thus, prevents cells' adhesiveness [25, 120]. In addition, resveratrol delays cell senescence via PI3K-Akt pathway in endothelial progenitor cells [115].

Summary and conclusions

The p66Shc is a mitochondrial protein mediating oxidative stress. The inhibition of p66Shc reduces oxidative stress, suggesting that p66Shc is a promising target to reduce ROS-mediated cardiovascular disease. SIRT1 is a protein sensitive to energy change in metabolism and improves cell survival and functions by deacetylating regulatory proteins. Up-regulation of SIRT1 exhibits multiple beneficial effects on endothelial dysfunction especially in diabetes. It may be considered optimistic to assume that simply down-regulating p66Shc, up-regulating SIRT1, or a combination of the two will effectively slow down aging in humans and

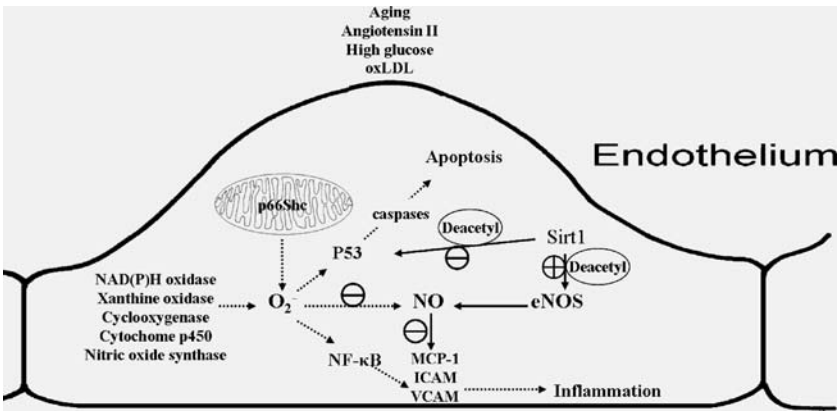

Fig. 4 Schematic representation of the endothelium and some of its key derived vasoactive substances. Different stress stimuli (e.g., glucose, oxLDL, and angiotensin II) and occurrence of aging enhance the production of $O2^-$ and determine endothelial dysfunction. p66Shc is principally located in the mitochondria where it contributes to the production of $O2^-$, which scavenges NO, and activates NF-κB and p53. Sirt1 deacetylates nitric oxide synthase, thus, restores NO availability. Sirt1 also deacetylates p53 and consequently, reduces cell apoptosis. The symbol (⊕) indicates activation while (⊖) indicates inhibition. *oxLDL* oxidized low density lipoprotein, *NOS* NO synthase, *NO* nitric oxide, *MCP-1* monocyte chemotactic protein-1, *ICAM* intercellular adhesion molecule, *VCAM* vascular cells adhesion molecule, *NF-κB* nuclear factor-kappa B, *NADPH* nicotinamide adenine dinucleotide phosphate-oxidase, *Deacetyl* deacetylation

shift the pathophysiological imbalance towards a normalized condition. Nevertheless, these recently discovered target proteins offer insights to better characterize underlying mechanisms of cardiovascular diseases and aging (Fig. 4).

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